**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 18880**

**Columns: Topic Highlights**

**2015 Advances in Cirrhosis**

**Ultrasound-based elastography for the diagnosis of portal hypertension in cirrhotics**

Şirli R *et al*. Elastography in cirrhosis

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**Author contributions:** Şirli R designed the research regarding the paper and wrote the manuscript; Şirli R, Sporea I, Popescu A and Dănilă M performed research; Sporea I, Popescu A and Dănilă M revised and completed the manuscript; all authors approved the final version of the manuscript.

**Conflict-of-interest statement:** None of the authors have any conflicts of interest regarding this paper.

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**Received:** April 28, 2015

**Peer-review started:** May 6, 2015

**First decision:** June 2, 2015

**Revised:** July 11, 2015

**Accepted:** August 30, 2015

**Article in press:**

**Published online:**

**Abstract**

Progressive fibrosis is encountered in almost all chronic liver diseases. Its clinical signs are diagnostic for advanced cirrhosis, but compensated liver cirrhosis is harder to diagnose. Liver biopsy is still considered the reference method for staging the severity of fibrosis, but due to its drawbacks (inter and intra-observer variability, sampling errors, unequal distribution of fibrosis in the liver, and risk of complications and even death), non-invasive methods were developed to assess fibrosis (biological and elastographic). Elastographic methods can be ultrasound-based or magnetic resonance imaging-based. All ultrasound-based elastographic methods are valuable for the early diagnosis of cirrhosis, especially Transient Elastography (TE) and Acoustic Radiation Force Impulse (ARFI) elastography, which have similar sensitivities and specificities, although ARFI has better feasibility. TE is a promising method for predicting portal hypertension in cirrhotic patients, but it cannot replace upper digestive endoscopy. The diagnostic accuracy of using ARFI in the liver to predict portal hypertension in cirrhotic patients is debatable, with controversial results in published studies. The accuracy of ARFI elastography may be significantly increased if spleen stiffness is assessed, either alone or in combination with liver stiffness and other parameters. Two-dimensional shear-wave elastography, the ElastPQ technique and strain elastography all need to be evaluated as predictors of portal hypertension.

**Key words:** Portal hypertension; Transient elastography; Acoustic radiation force impulse elastography; Two-dimensional shear-wave elastography

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**Core tip:** Ultrasound-based elastographic methods are being used more and more for the non-invasive assessment of liver fibrosis, with very good accuracy in diagnosing cirrhosis. Transient elastography is a promising method for predicting portal hypertension in cirrhotics, but it cannot replace upper digestive endoscopy. The diagnostic accuracy of employing Acoustic Radiation Force Impulse Elastography in the liver to predict portal hypertension is debatable. It may be significantly increased if spleen stiffness is assessed, whether alone or in combination with liver stiffness and other parameters. Two-dimensional shear-wave elastography, the ElastPQ technique and strain elastography all need to be evaluated as predictors of portal hypertension.

Şirli R, Sporea I, Popescu A, Dănilă M. Ultrasound-based elastography for the diagnosis of portal hypertension in cirrhotics. *World J Gastroenterol* 2015; In press

INTRODUCTION

Almost all chronic liver diseases can evolve to liver cirrhosis, which is characterized by profound changes in liver structure that are caused by pseudo-nodule formation as a consequence of necrosis and fibrosis. The main causes of chronic liver disease are infections with hepatitis B and C viruses, but a rising incidence of alcoholic and non-alcoholic steatohepatitis (ASH and NASH, respectively) has been observed in developed countries[1]. Published data from the World Health Organization (WHO), state that 160 million individuals are infected with hepatitis C virus (HCV), representing 2.35% of the population, with the highest prevalence in Egypt (20%) and the lowest prevalence in northern European countries (< 0.5%)[2]. It is estimated that up to 30% of HCV patients will develop cirrhosis at least 10 years after diagnosis[3]. The prevalence of hepatitis B virus is even higher, with more than 240 million chronically infected patients; the highest prevalence is reported in sub-Saharan Africa and South-East Asia (5%-10% in adults) and the lowest is reported in Western Europe and North America (< 1%)[4]. It is estimated that 650000 deaths occur each year as a consequence of liver cirrhosis and hepatocellular carcinoma secondary to chronic hepatitis B infection[4]. Alcoholic cirrhosis is also a major cause of disease burden and death. In 2010, 493300 deaths were attributable to alcoholic cirrhosis worldwide (7.2 per 100000 people; 47.9% of all liver cirrhosis deaths)[5]. In Europe, also in 2010, 43500 deaths were caused by alcoholic cirrhosis[5].More than 5,500 liver transplants are performed in Europe each year, 59% of them for liver cirrhosis; of these, 33% come from a purely alcoholic etiology, and 5% come from a mixed alcoholic and viral etiology[6].

It is easy to diagnose decompensated liver cirrhosis in which clinical, biologic and ultrasound signs are evident. However, the most important aspect of prognosis is the differentiation between compensated cirrhosis and chronic hepatitis. Until a few years ago, liver biopsy (LB) was considered to be the reference method for staging chronic hepatitis[7]. However, because it has some drawbacks, including sampling variability and intra- and interobserver variability[8-10], and most importantly because it is an invasive method, noninvasive tests were developed to stage chronic hepatitis, ergo, to diagnose cirrhosis. These noninvasive tests are either serologic, including the FibroTest and ActiTest[11], or elastographic.

Elastographic methods evaluate a property that is intrinsic in every tissue: elasticity, which is the capacity of a tissue to deform and then return to its initial shape when an extrinsic force is applied. Regarding the liver, more fibrosis means that the tissue is less elastic (stiffer). Liver stiffness (elasticity) can be evaluated by magnetic resonance elastography[12,13] or by ultrasound-based elastographic methods[14,15]. According to the guidelines and recommendations published by the European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) regarding the clinical use of ultrasound elastography, ultrasound-based elastographic methods can be classified as the following: (1) strain elastography (quasi-static, qualitative elastography), which includes Real Time-Elastography (RT-E); (2) Shear-Wave Elastography (SWE) (quantitative elastography), which includes a: Transient Elastography (TE); b: Point SWE[Acoustic Radiation Force Impulse Elastography (ARFI) and the ElastPQ technique]; and c: real-time SWE[including two-dimensional SWE (2D-SWE) and three-dimensional SWE (3D-SWE)][14,16,17].

It is a known fact that patients with advanced cirrhosis have shorter survival rates due to severe complications such as: portal hypertension (development of esophageal varices - EV), hepatocellular carcinoma (HCC), and hepato-renal syndrome. Thus, it would be advantageous to identify the patients who are at risk for these complications and to screen them: for EV by upper endoscopy and for HCC by ultrasound.

Portal hypertension is one of the most feared complications of cirrhosis. It can lead to the development of esophageal and gastric varices (EV and GV, respectively) and upper digestive bleeding due to variceal rupture. The best method to assess bleeding risk is measurement of hepatic venous pressure gradient (HVPG), available only in specialized centers, and an invasive procedure. In clinical practice, the size of EV is used to assess bleeding risk. According to Baveno V and AASLD Consensuses, primary prevention of variceal bleeding should be applied to patients with large (grade 2 or 3) EV[18,19]. To diagnose clinically significant EV (large, grade 2 or 3 EV), a screening program inclusive of periodic upper digestive endoscopy should be implemented. However, repeated endoscopies are often poorly accepted by patients and are also expensive. Thus, it would be very useful to find a non-invasive, inexpensive technique to predict the occurrence of significant varices and the risk of bleeding. It was logical to evaluate the proficiencies of various elastographic methods in this regard because they have been proven to be very accurate in predicting the presence of cirrhosis.

***TE***

TE was the first elastographic method that was developed to evaluate LS as a predictor for fibrosis[20]. It uses a FibroScan device (Echosens, Paris, France) that includes a special ultrasound probe (3.5 MHz for the standard M probe) integrated into a piston that "punches" the body surface. The "punch" generates shear waves that propagate into the liver. Their velocity is measured by pulse-echo ultrasound acquisition and is proportional to LS, increasing in parallel with LS. The FibroScan device displays a Young's modulus, expressed in kilopascals (kPa), which is proportional to the shear-wave velocity[14,16,17]. Measured values range from 2.5 to 75 kPa.

Liver stiffness is measured in the right liver lobe, in fasting patients. The software automatically rejects measurements with an inconsistent vibration shape or follow-up. For a reliable assessment, ten valid shots should be obtained, and the median value of these measurements should be considered indicative of the LS value. The technical quality parameters that should be considered for correct LS measurements include the success rate (SR) and the interquartile range (IQR). SR is the percentage of valid shots from the total number of shots, while IQR is a measure of variability and is calculated as the difference between the 75th and the 25th percentile of obtained values. Thus, TE measurements are regarded as unreliable if 10 valid shots cannot be obtained or if the IQR is higher than 30% of the median value and/or the SR is lesser than 60%. If no valid shots are obtained, TE measurement is considered failed[21].

Several published meta-analyses have demonstrated that LS measurement by TE is a reliable method for diagnosing cirrhosis, with a pooled sensitivity ranging from 84.45% to 87% and a pooled specificity ranging from 91% to 94.69%[13,22]. In the most recent meta-analysis, for a mean optimal cut-off of 15 kPa, the summary sensitivity was 0.83 for diagnosing cirrhosis with summary specificity of 0.89[23]. However, the cut-off values for diagnosing cirrhosis may vary according to its etiology[24]. Published studies have found the following cut-offs: in HCV infection - 12.5 kPa[25], in HBV infection - 13.4 kPa[26], in NAFLD - 10.3 kPa[27], in ASH - 22.4 kPa[28], and in cholestatic chronic diseases - 17.3 kPa (primary sclerosing cholangitis and primary biliary cirrhosis)[29].

Several studies were published regarding the correlation between TE measurements and HVPG (Table 1). The first studies were performed in rather small numbers of patients. In an Italian study on a small number of patients, the AUROC for predicting HVPG ≥ 10 mmHg was 0.99 with 97% sensitivity, while for predicting HVPG ≥ 12 mmHg the calculated AUROC was 0.92 with 94% sensitivity. The calculated cut-offs were 13.6 kPa for HVPG ≥ 10 mmHg and 17.6 kPa for HVPG ≥ 12 mmHg. The cut-off was also 17.6 kPa for predicting any EV (90% sensitivity, AUROC 0.76)[30].

In a French study, TE accurately predicted HVPG > 10 mmHg (significant portal hypertension); the AUROC was 0.945. The calculated cut-off was 21 kPa[31]. In another French study by the same group, which followed up for 2 years 100 patients evaluated by TE and HVPG, similar performances of TE and HVPG for predicting portal hypertension were observed, with AUROCs of 0.830 and 0.845, respectively. During the follow-up, none of the patients with LS values lower than the calculated cut-off (21.1 kPa) had complications of portal hypertension, *vs* 47.5% of those with values higher than the cut-off[32].

In an Austrian study including 122 cirrhotics with EV, a stronger correlation was observed between LS measurements by TE and HVPG in patients with HVPG lower than 12 mmHg (*r =* 0.951) *vs* those with HVPG higher than 12 mmHg (*r =* 0.538) and that the correlation improved in patients who were hemodynamic responders to beta-blocker therapy (*r =* 0.864), while in non-responders it remained the same (*r =* 0.535)[33]. The calculated cut-off to discriminate between patients with grade 1 EV and those with grade 2 or 3 EV was 47.5 kPa, with good sensitivity (80.6%) but rather poor specificity (47.7%)[33].

The same Austrian group evaluated 502 patients by TE and HVPG. They observed a strong correlation between LS assessment by TE and HVPG (*r =* 0.794; *p* < 0.0001). The correlation was stronger in cirrhotics with viral etiology (*r =* 0.838) than in those with alcoholic disease (*r =* 0.756). For a cut-off of 18 kPa, TE had an 86% positive predictive value and an 80% negative predictive value in identifying cirrhotics with clinically significant portal hypertension (CSPH: HPVG ≥ 10 mmHg)[34].

Recently published studies have also demonstrated a good correlation between TE and HVPG. In a study from 2014, the calculated cut-off to predict CSPH was 16.8 kPa, with 89.7% sensitivity and 75% specificity (AUROC = 0.870)[35]. The same group demonstrated that if new reliability criteria for TE were used[very reliable measurements (IQR/M < 0.1), reliable (IQR/M < 0.3, or > 0.3 if TE < 7.1 kPa) and poorly reliable (IQR/M > 0.3, if TE > 7.1 kPa), where M= the median value], the number of patients who could be evaluated increased (83.2% *vs* 71.6%) without affecting the accuracy of identifying those with CSPH[88.9% (AUC = 0.957) *vs* 89.8% (AUC = 0.962) for a cut-off of 16.1 kPa][36].

As mentioned above, HPVG measurement is an invasive procedure and is not available at many centers; therefore, in clinical practice, upper digestive endoscopy is used to diagnose EV as a sign of portal hypertension. The first published studies demonstrated that LS values lower than 19 kPa had a high negative predictive value for significant EV (grade 2 and 3)[37], with cut-offs varying from 27.5 to 47.2 kPa[38,39]. Additionally, for predicting esophageal bleeding, the calculated cut-off was 62.7 kPa[38].

Predictive LS values for grade 2 and 3 EV were assessed according to cirrhosis etiology (Table 2). The cut-offs were higher alcoholic cirrhosis (47.2 kPa, AUROC = 0.77, 63.6% specificity, 84.6% sensitivity, 92.5% negative predictive value and 44% positive predictive value) than in patients with viral etiology (19.8 kPa, AUROC = 0.73, 55.1% specificity, 88.9% sensitivity, 96.4% negative predictive value and 26.7% positive predictive value)[39]. A similar phenomenon was observed in a study from our group that was conducted on almost 700 patients. In our study, the best LS cut-off for significant EV was 32.5 kPa (AUROC = 0.836) in patients with alcoholic cirrhosis compared with 24.8 kPa (AUROC = 0.867) in those with viral cirrhosis[40].

In a study from 2009 on HCV cirrhosis, Castera *et al* calculated a cut-off of 21.5 kPa to predict the occurrence of EV, but it had only 76% sensitivity and 78% specificity, thus it was concluded that TE cannot be a replacement for upper endoscopy for the diagnosis of EV[41]. In a smaller, more recent study that compared TE with Forns Index, FIB-4 and Lok score for the prediction of grade 2 and 3 EV in patients with HCV cirrhosis, for a 22.4 kPa cut-off, TE showed the highest accuracy (80%) (AUROC 0.801)[42].

Chen *et al* evaluated 238 patients with HBV cirrhosis by TE and upper digestive endoscopy. In patients with significant cytolysis (≥ 5 × upper limit of normal), for a 36.1 kPa cut-off, TE had 100% negative predictive value with 72.7% positive predictive value for predicting grade 2 and 3 EV, with an AUROC of 0.93[43].

In 2012 Castera published a review article that evaluated only small studies (47-211 patients) with contradicting results: cut-offs for predicting significant EV 19.8 - 48 kPa; with AUROCs 0.73-0.87. Castera concluded that “diagnostic performances of TE are acceptable for the prediction of clinically significant portal hypertension but far from satisfactory to confidently predict the presence of EV in clinical practice and to screen cirrhotic patients without endoscopy“[44].

This review did not include a Romanian study conducted on 1000 consecutive cirrhotics[45]. For an optimal cut-off of 31 kPa, we calculated a 76.2% negative predictive value for at least grade 2 EV and a positive predictive value of 71.3%. If the cut-off for at least grade 2 EV was chosen so that the positive predictive value was higher than 85% (> 40 kPa), we calculated 77.8% sensitivity, 68.3% specificity, 86% positive predictive value, with 55% negative predictive value. If the cut-off was chosen so that the negative predictive value was close to 90% (17.1 kPa), we calculated the negative predictive value to be 89.3%, with 43.2% positive predictive value, 92.6% sensitivity and 33.5% specificity for at least grade 2 EV[45]. Thus, according to our calculations, patients with LS values higher than 40 kPa will have significant portal hypertension in at least 8/10 cases and should receive prophylactic beta-blocker treatment without undergoing endoscopy. Considering that for the 40 kPa cut-off the negative predictive value was 54.9%, 5/10 cases will have significant (grade 2 and 3) EV, thus we recommend endoscopic evaluation. For the 17.1 kPa criterion the negative predictive value for significant EV was 89.3% (1 in 10 patients), thus we do not recommend endoscopic assessment[45].

Finally, a method's value is demonstrated by meta-analyses. Regarding TE and portal hypertension, a meta-analysis that included 18 studies with more than 3,500 patients was published in 2013[46]. It showed that TE had a 0.90 summary sensitivity and a 0.79 summary specificity (AUROC = 0.93) for predicting CSPH (HVPG ≥ 10 mmHg), a 0.87 summary sensitivity and a 0.53 summary specificity (AUROC = 0.84) for predicting the occurrence of any EV, and a 0.86 summary sensitivity and a 0.59 summary specificity (AUROC = 0.78) for predicting significant (grade 2 and 3) EV. The conclusion was that, due to the low specificity of this method, TE cannot replace upper gastrointestinal endoscopy for EV screening[46].

Spleen stiffness (SS) measurement by TE was also assessed as predictor of portal hypertension based on the idea that splenomegaly is one of the clinical signs of cirrhosis. Several studies found a good correlation between SS and LS by TE in patients with cirrhosis and also between SS and the presence of EV[47,48] or HVPG[49].

In a cohort of 200 cirrhotics, SS values higher than 40.8 kPa had 94% sensitivity, 76% specificity, 91% positive predictive value and 84% negative predictive value for the presence of any EV. Also, SS by TE was significantly correlated with HVPG (*r =* 0.433, *P =* 0.001). When combining LS (cut-off 27.3kPa) and SS (cut-off 40.8 kPa), the accuracy of TE in predicting EV was 90%[50].

Because in many cases a maximum value of 75 kPa is obtained when assessing SS in patients with cirrhosis, the idea of using a modified software version for SS assessment by TE was explored. Using this modified software, which is not commercially available, mSS values of up to 150 kPa could be obtained by TE. In a series of 80 HCV cirrhotics, mSS accurately predicted grade 3 EV: the cut-off was 75 kPa, with 100% sensitivity, 69.01% specificity, 100% negative predictive value and 29% positive predictive value, with an AUROC of 0.903[51]. Similar results were obtained in another study in which multivariate analysis demonstrated that mSS was the only independent factor associated with grade 2 and 3 EV. The cut-off was 54 kPa, with 80% sensitivity, 70% specificity, and an AUROC of 0.82[52].

Finally, the EFSUMB guidelines on the use of elastography state that: "TE has some value for predicting the occurrence of complications of liver cirrhosis, portal hypertension, HCC and liver-associated mortality. It cannot replace upper gastrointestinal endoscopy for identifying patients with varices"[15].

***ARFI***

ARFI is a point shear-wave elastographic technique that measures LS as a predictor of fibrosis. ARFI was first developed by Siemens and was integrated into a standard ultrasound machine (Acuson S2000TM, Siemens, Erlangen, Germany); it is also available in newer models. It evaluates LS in a 10/5 mm region of interest (ROI), placed by the operator in a region free of large vessels, while performing B-mode real-time examination. The probe automatically produces a 262 µs, 2.67 MHz acoustic “push” pulse that induces shear-waves into the liver, which are tracked using ultrasound correlation-based methods[53]. Shear-waves speed is quantified using a patented application of ARFI technology (Virtual Touch Tissue Quantification, VTQ). The measurement result is displayed on the screen (expressed in m/s), together with the measurement depth.

Scanning is performed with minimal scanning pressure, via an intercostal approach on the right liver lobe, approximately where a liver biopsy would be performed, in fasting patients in a dorsal decubitus position to avoid cardiac motion. Measurements should be performed 1-2 cm under the capsule[17,54-56]. No recommendations were made by the manufacturer regarding the quality criteria that should be used, but published papers showed a better correlation with histological fibrosis if quality criteria similar to those from TE were used (SR > 60% and especially IQR ≤ 30%)[17,57,58].

Several studies have proven that ARFI elastography is reliable technique to predict cirrhosis when compared to liver biopsy, with cut-offs ranging from 1.55 to 2 m/s and AUROCS ranging from 0.89 to 0.937[54,59-62]. Additionally, when ARFI elastography was compared to TE with liver biopsy as the reference method, it had similar performance to TE in diagnosing cirrhosis[61,62].

Several meta-analyses have confirmed that ARFI is a valuable method for diagnosing cirrhosis, with mean diagnostic accuracies reported as AUROCs of 0.93[63] and 0.91[64], which are comparable to TE[63,65].

Published studies showed controversial results regarding *liver* assessment by ARFI elastographyas a predictor of portal hypertension (Table 3). A study from our group showed no significant differences between mean LS by ARFI in patients with no or grade 1 EV (2.73 ± 0.71 m/s) *vs* those with grade 2 and 3 EV (2.8 ± 0.71 m/s, *P =* 0.49), nor between those that had a history of variceal bleeding (2.78 ± 0.81) *vs* those with no bleeding history (2.77 ± 0.7 m/s, *P =* 0.99)[66]. Additionally, another study from Romania showed a rather poor performance of ARFI elastography in predicting large EV, with an AUROC of only 0.596[67], which is a similar result to that from another European study in which the AUROC for predicting large EV was 0.58[68].

Much better results were obtained in Asian studies (Table 3). In a Japanese study, the LS cut-off by ARFI for predicting any EV was 2.05 m/s (83% sensitivity, 76% specificity, AUROC 0.89), while for high-risk EV the cut-off was 2.39 m/s (81% sensitivity, 82% specificity, AUROC 0.868)[69].

An European study showed a good correlation (*r* =  0.646; *p* < 0.001) between LS measurements by ARFI elastography and HVPG. The calculated cut-off to predict CSPH was 2.58 m/s (71.4% sensitivity, 87.5% specificity, AUROC 0.855)[35].

Similar to TE, spleen stiffness (SS) assessment by ARFI elastography was evaluated as a predictor of portal hypertension, also with controversial results.

In a study by Rifai *et al*[70], SS performed significantly worse than LS in predicting CSPH (AUROC 0.68 *vs* 0.90), but it must be considered that the LS cut-off calculated to predict CSPH was only 1.67 m/s, which is much lower than that proposed for diagnosing liver cirrhosis[59-62]. The optimal SS cut-off for predicting CSPH was 3.29 m/s, but with rather poor specificity and sensitivity: 73% and 47%, respectively[70]. In a smaller study on only 33 cirrhotic HCV patients, in which only 12 had EV, it was found that evaluating SS by ARFI correlates with the presence of ascites but not with the presence of EV[71].

In a study by Vermehren *et al*, the situation was reversed. It was demonstrated by multiple logistic regression analysis that SS by ARFI performed better than LS by ARFI for predicting the presence of large EV, even if the AUROCs of ARFI of the liver and ARFI of the spleen were similar (0.58 for both)[68].

Another study measured liver and spleen stiffness by ARFI before and after placement of a transjugular intrahepatic portosystemic shunt (TIPS). The mean LS determined by ARFI did not differ before and after TIPS placement, while SS significantly decreased after TIPS placement, at 3.65 ± 0.32 m/s before *vs* 3.27 ± 0.30 m/s after TIPS (*p* < 0.001)[72].

In a study from our group, we combined several parameters to improve the accuracy of ARFI elastography for predicting grade 2 and 3 EV. LS and SS values by ARFI as well as the presence of ascites were associated with significant EV by univariant analysis. Using multiple regression analysis, the following formula to predict at least grade 2 EV was calculated:Prediction of significant EV (Pred EV2-3) score = -0.572 + 0.041 x LS (m/s) + 0.122 x SS (m/s) + 0.325 x ascites (1-absent, 2-present). The optimal Pred EV(2-3) cut-off for predicting grade 2 and 3 EV was 0.395, with 69.6% accuracy (AUROC 0.721)[67].

Considering these conflicting results, further studies and meta-analysis are necessary to assess the real value of LS and SS by ARFI elastography as predictors portal hypertension in cirrhotics, either alone or in combination. Published studies have not explained why TE can predict portal hypertension while ARFI cannot. One explanation may be that there is a wider range for TE above the cut-off for cirrhosis (approximately 12.5-13.5 kPa up to 75 kPa) than for ARFI (approximately 1.8-2 m/s up to 5 m/s).

***2D-SWE***

2D-SWE is an elastographic method integrated into an AixplorerTM ultrasound machine (SuperSonic Imagine S.A., Aix-en-Provence, France). To obtain a stiffness measurement, tissue is stimulated by an acoustic "push" pulse generated by the transducer, which generates shear-waves in the tissue. Ultrafast imaging technology allows the acquisition of raw radiofrequency data with a very high frame rate, of up to 5000 frames/s, which enables shear-wave speed estimation by a Doppler-like acquisition over a ROI, which is used for tissue stiffness assessment. Elasticity is displayed as a color-coded image superimposed on a standard, grey-scale B-mode image: red denotes stiffer tissues and blue denotes softer tissues. Additionally, a numerical value is displayed together with the standard deviation of the measured elasticity, either in kPa or in m/s[14,16,17,73,74].

2D-SWE measurements are performed under fasting conditions via an intercostal approach using 3-5 acquisitions, after which a mean value is calculated[15]. Starting from the first published studies regarding 2D-SWE, this method has proven to be accurate for diagnosing cirrhosis. In hepatitis C patients, the reported AUROCs were 0.94[75] and 0.98[76]. The cut-off value was 10.4 kPa[76]. In hepatitis B patients, the cut-off for cirrhosis was 10.1kPa (AUROC 0.98)[77]. In a recently published study in hepatitis B patients, the AUROC for predicting cirrhosis was 0.945 in the index cohort and 0.967 in the validation cohort for a cut-off of 11.7 kPa[78]. In mixed etiology patients, the cut-off for 2D-SWE in predicting cirrhosis was 11.5 kPa (AUROC 0.914)[79]. In a very recent study, the AUROC of 2D-SWE in predicting cirrhosis was also very good at 0.926[80].

Regarding 2D-SWE as a tool to predict portal hypertension, we found only two published studies, both in 2015. In the one performed by Kim *et al*, LS measurement by 2D-SWE was used to predict portal hypertension assessed by HVPG measurement. For a cut-off value of 15.2 kPa, 2D-SWE accurately predicted CSPH (HVPG > 10 mmHg), with 85.7% sensitivity and 80% specificity (AUROC 0.819)[81]. In a study by Procopet *et al*[81], a very good accuracy of LS by 2D-SWE was observed when quality technical parameters were taken into consideration (SD/median LS ≤ 0.10 for depth of measurement < 5.6 cm and SD/median LS > 0.10 for depth of measurement ⩾ 5.6 cm). In this category of patients, the best cut-off to predict CSPH was 15.4 kPa (AUROC = 948, with sensitivity and specificity both higher than 90%).

Further larger studies and meta-analyses are needed to assess 2D-SWE as a predictor of portal hypertension.

***Strain elastography***

Although strain elastography was the original elastographic method used to assess tissue stiffness and is currently available in most high-end ultrasound machines, its value in assessing liver stiffness as a predictor of fibrosis severity is not yet defined due to unstandardized methodology. Initially, hand compression was used for tissue deformation, but in newer systems heartbeats are used to stress the tissue. Elasticity is displayed as a color-coded image superimposed on a standard, gray-scale, B-mode image: red denotes softer tissues and blue denotes stiffer tissues. In newer systems, a histogram and 11 parameters are also displayed[17]. Recent studies showed promising results when using strain elastography to predict cirrhosis using both elastic ratios[82,83] and average strain histograms[84]. No data are available regarding the use of elastic ratios and average strain histograms obtained by strain elastography for the assessment of portal hypertension.

***ElastPQ technique***

The ElastPQ technique is the newest elastographic method to appear on the market. It is also a point-SWE technique, which was developed by Philips, and is integrated into the iU22 ultrasound system (Philips Medical Systems, Bothell, WA, United States). An ultrasonic pressure wave generated by the transducer induces shear-waves in liver tissue, whose speed is measured by the Doppler functions of the system within an ROI that is placed by the operator in a desired location using B-mode standard ultrasound. A numeric value indicative of liver stiffness, which is expressed either in m/s or kPa, is displayed on the screen[17]. Promising results following the use of the ElastPQ technique to predict cirrhosis were obtained in both HCV and HBV patients[85-87]. No data are available regarding the predictive value of the ElastPQ technique for portal hypertension.

**Conclusion**

In conclusion, we suggest that all elastographic methods are reliable for the early diagnosis of cirrhosis, especially TE and ARFI, whose value has been proven by meta-analyses. While TE is a promising method to predict portal hypertension in cirrhotics, it cannot replace upper digestive endoscopy. The diagnostic accuracy of LS assessment by ARFI in predicting portal hypertension in cirrhotics is debatable. The accuracy of ARFI elastography may be significantly improved if spleen stiffness is also assessed, either alone or in combination with liver stiffness and other parameters. 2D-SWE, the ElastPQ technique and strain elastography all need to be evaluated as predictors of portal hypertension.

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**P-Reviewer:** Abenavoli L, Tai DI **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 predictive value of Transient Elastography in the liver for clinically significant portal hypertension**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | HPVG ≥ 10 mmHg | | | | HVPG ≥ 12 mmHg | | | |
| **Cut-off (kPa)** | **AUROC** | **Se (%)** | **Sp (%)** | **Cut-off (kPa)** | **AUROC** | **Se (%)** | **Sp (%)** |
| Vizzutti *et al*[30], *Hepatology* 2007 | 13.6 | 0.99 | 97 | 92 | 17.6 | 0.92 | 94 | 81 |
| Bureau *et al*[31], *Aliment Pharmacol Ther* 2008 | 21 | 0.945 | 89.9 | 93.2 | - | - | - | - |
| Reiberger *et al*[34], *Wien Klin Wochenschr.*2012 | 18 | 0.871 | 83.4 | 82.2 | 20 | 0.790 | 84.2 | 80.7 |
| Salzl *et al*[35], *Ultraschall Med*. 2014 | 16.8 | 0.870 | 89.7 | 75 | - | - | - | - |
| 1Shi *et al*[46], *Liver Int.* 2013 | - | 0.93 | 90 | 79 | - | - | - | - |

1Meta-analysis: HSROC and summary Se and summary Sp are presented. HPVG: Hepatic venous pressure gradient; Se: Sensitivity; Sp: Specificity; AUROC: Area under the receiver operating characteristics curve.

**Table 2 predictive value of Transient Elastography in the liver for esophageal varices**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | At least grade 1 EV | | | | At least grade 2 EV | | | |
| **Cut-off**  **(kPa)** | **AUROC** | **Se (%)** | **Sp (%)** | **Cut-off**  **(kPa)** | **AUROC** | **Se (%)** | **Sp (%)** |
| Nguyen-Khac *et al*[39] *Alcohol Clin Exp Res* 2010 | - | - | - | - | 47.2  (alcoholic) | 0.77 | 84.6 | 63.6 |
| Nguyen-Khac *et al*[39] *Alcohol Clin Exp Res*. 2010 | - | - | - | - | 19.8  (viral) | 0.73 | 88.9 | 55.1 |
| Sporea *et al*[40] *Med Ultrason*. 2013 | - | - | - | - | 32.5  (alcoholic) | 0.836 | 85 | 74.6 |
| Sporea *et al*[40] *Med Ultrason*. 2013 | - | - | - | - | 24.8  (viral) | 0.867 | 81 | 80.7 |
| Castéra *et al*[40] *J Hepatol*. 2009 | 21.5  (HCV) | 0.84 | 76 | 78 | 30.5  (HCV) | 0.87 | 77 | 85 |
| Sporea *et al*[45] *World J Gastroenterol*. 2011 | 31 | 0.780 | 83 | 62 | - | - | - | - |
| 1Shi *et al*[46] *Liver Int.* 2013 | - | 0.84 | 87 | 53 | - | 0.78 | 0.86 | 0.59 |

1Meta-analysis: HSROC and summary Se and summary Sp are presented. EV: Esophageal varices; Se: Sensitivity; Sp: Specificity; AUROC: Area under the receiver operating characteristics curve.

**Table 3 predictive value of Acoustic Radiation Force Impulse Elastography in the liver for esophageal varices**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | At least grade 1 EV | | | | At least grade 2 EV | | | |
| **Cut-off**  **(m/s)** | **AUROC** | **Se (%)** | **Sp (%)** | **Cut-off**  **(m/s)** | **AUROC** | **Se (%)** | **Sp (%)** |
| Bota *et al*[67], *Ann Hepatol*. 2012 | - | - | - | - | 2.25 | 0.596 | 93.4 | 28.9 |
| Morishita *et al*[69] *J Gastroenterol* | 2.05 | 0.89 | 83 | 76 | 2.39 | 0.868 | 81 | 82 |

EV: Esophageal varices; Se: Sensitivity; Sp: Specificity; AUROC: Area under the receiver operating characteristics curve.